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THE CLINICAL USE OF FOLIC ACID

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THE CLINICAL USE OF FOLIC ACID

The experimental and clinical researches which have accompanied the discovery and synthesis of "folic acid," newest member of the vitamin B complex, have culminated in the achievement of a long-sought goal—a nutritional factor which is effective in the control of the various macrocytic anemias. Success in the treatment of these anemias with "folic acid" has been reported. The question arises—is then "folic acid," specifically synthetic *L. casei* factor, the assiduously sought "pure extrinsic factor" which Moore *et al* (1) hoped to test on their anemia patients in order to obtain final proof of their theory of the cause of the macrocytic anemia of pellagra. Is it the cheap remedy so desperately sought by the British? If it is the extrinsic factor, why is it effective when administered as the sole therapeutic agent in certain cases of pernicous anemia as well (1a)? Might it be the anti-pernicious anemia factor itself — the erythrocyte maturing factor? Or, might it actually be none of these, merely being an independent substance essential for the synthesis or effective utilization of the anti-anemia factor(s)? The answers to these thought-provoking questions appear to be excitingly near at hand. As yet, no claims have been made for "folic acid" other than its actual record of performance as noted in clinical studies; it has been stated by Vilter *et al* (2) as a matter of fact, that alhough "synthetic folic acid (*L. casei* factor) is a potent hematopoietic agent, it is suspected that it should be no more effective than liver extract in the treatment of macrocytic anemia."

Clinical Findings:

Anemia: In a preliminary note, Spies *et al* (3) reported their observations on the hematological responses of 9 cases of unclassified macrocytic anemia to administration of the newly synthesized *L. casei* factor. Five of the patients, hospitalized with "macrocytic anemia in relapse" received intravenous injections of the *L. casei* factor in total doses ranging from 20 to 360 milligrams over periods of from one to eighteen days. The other four patients received the vitamin orally in 50 milligram doses two or three times a day. Of the first group of patients, four had previously responded favorably to liver therapy; the fifth had never been treated with liver. All five were placed on carefully controlled, meat-free diets (to reduce to a minimum possible sources of the extrinsic factor) during treatment with "folic acid". Within three or four days after the first injections all of the patients exhibited a characteristic subjective sensation of well-being similar to that observed in anemia patients in relapse after liver therapy. Reticulocyte responses were obtained in all five, reaching a maximum in about six to ten days. The reticulocytosis was followed in each case by a slight increase in the number of red blood cells and in their hemoglobin content (Table 1).

EFFECT OF PARENTERAL ADMINISTRATION OF FOLIC ACID

Case	Initial: Millions Red Cells	Initial: Hg. Gm.	Reticulocytosis: First Day of Rise	Reticulocytosis: Day of Peak	Reticulocytosis: Per Cent at Peak	Duration of Administration (days)	Total Dose Mg.
1	1.82	7.7	4	6	10.6	1	50
2	2.54	8.7	4	7	9.0	1	20
2a	2.15	8.8	4	8	14.8	18	360
3	1.61	6.2	8	10	11.0	18	360
4	1.90	9.2	6	8	14.5	14	280
5	1.95	7.0	6	8	6.5	13	260

Table 1

Cases 1 and 2 were given single injections of the substance and the subsequent reticulocyte rise subsided eleven days from the time of injection. Cases 3, 4, and 5 were given 20 mg. *L. casei* factor intravenously daily for 18, 14, and 13 days. On this regime the rise was more sustained. A slight increase in the number of red blood cells and hemoglobin content occurred in each case.

Ten days after the reticulocytes fell to the control level in Case 2 (following the single injection), 20 mg. *L. casei* factor was again injected, on this occasion intramuscularly and at daily intervals. Reticulocytes again increased, reaching a peak of 14.8 per cent on the eighth day. This response is noted in the table under Case 2a.

Similar responses were obtained when *L. casei* factor was administered orally (Table 2).

EFFECT OF ORAL ADMINISTRATION OF FOLIC ACID

Case	Millions Red Cells: Initial	Millions Red Cells: Twelfth Day	Hemoglobin Gm.: Initial	Hemoglobin Gm.: Twelfth Day	Reticulocytosis: First Day of Rise	Reticulocytosis: Day of Peak	Reticulocytosis: Per Cent at Peak
6	1.64	3.21	7.1	9.7	4	5	19.2
7	2.01	3.10	9.2	10.2	5	8	10.0
8	2.01	2.69	8.3	10.0	3	5	19.8
9	2.35	3.35	7.8	9.1	4	7	21.4

Table 2

From the results shown in the tables, the authors concluded that "persons with macrocytic anemia in relapse have a significant hemopoietic response following the administration of synthetic folic acid. This response follows either parenteral injection or oral administration (of course, cases will be found that do not absorb satisfactorily from the alimentary tract, and they will not respond). In every instance the number of reticulocytes increased in the peripheral blood, and the red blood cell counts and hemoglobin content rose toward normal levels."

One month later, Vilter, Spies and Koch (2) reported more detailed studies on the use of "folic acid" in macrocytic anemia. Case reports on fourteen patients were presented, this time most of the cases being differentially diagnosed, where possible, as pernicious anemia or nutritional macrocytic anemia. Table 3 summarizes results obtained in five patients receiving "folic

EFFECT OF PARENTERAL ADMINISTRATION OF "FOLIC ACID" ON PERIPHERAL BLOOD IN MACROCYTIC ANEMIA

Case No.	RBC (Million)			Hg. (Gm)			Reticulocytes Per Cent			Dosage of Folic Acid		
	Initial	14 Days	Final (day)	Initial	14 Days	Final (day)	First Day of Rise	Day of Peak	Per Cent at Peak	Daily Dose mg.	No. of Days	Total mg.
1-A	2.54	2.21	2.18	8.7	9.9	8.9	4	7	9.0	20 I.V.	1	20
1-B	2.16	2.69	4.08 (40)	8.8	9.3	11.7 (40)	4	8	14.8	20 I.M.	18	360
2	1.82	2.23*	2.92 (22)	7.7	10.1	9.8 (22)	4	6	10.4	50 I.V.	1	50
3	1.95	2.59	3.22 (55)	7.0	9.8	11.0 (55)	6	8	6.4	20 I.V.	13	260
										100(0)	10	1000
4	1.96	2.92	3.54 (49)	7.8	11.7	12.1 (49)	6	8	14.6	20 I.V.	26	520
5	1.6f	1.58	1.58† (18)	6.2	8.0	8.0 (18)	7	10	11.0	20 I.V.	26	520

*Folic acid was given after a suboptimal response to an experimental liver fraction, the last dose of which was given 11 days previously.

†Reticulogen, 50 U.S.P. units given from the eighteenth through the twenty-third day produced further reticulocytosis and maximal regeneration.

Table 3

EFFECT OF ORAL ADMINISTRATION OF "FOLIC ACID" ON PERIPHERAL BLOOD IN MACROCYTIC ANEMIA

Case No.	RBC (Million)			Hg. (Gm)			Reticulocytes Per Cent			Dosage of Folic Acid			Remarks
	Initial	14 Days	Final (day)	Initial	14 Days	Final (day)	First Day of Rise	Day of Peak	Per Cent at Peak	Daily Dose mg.	No. of Days	Total mg.	
6	2.01	2.69	4.22 (40)	8.3	10.7	13.9 (40)	4	6	14.8	100	23	2300	Continued medication 100 mg. 2 x week
7	2.98	3.14	3.20 (20)	9.3	8.3	9.2 (20)	4	4	4.6	100 100*	10 10	1000 1000	
8	2.59	3.14	3.72 (21)	8.6	10.6	10.1 (21)	4	7	14.4	100	22	2200	Continued medication 100 mg. 2 x week
9	1.64	3.24	4.07 (19)	7.1	10.2	9.8 (19)	3	5	19.2	100	19	1900	
10	2.35	3.53	4.29 (48)	7.8	9.9	12.4 (48)	5	7	21.4	150	30	4500	Continued medication 100 mg. 2 x week
11	2.32	3.31	3.38 (21)	8.0	11.2	11.7 (21)	4	7	19.6	100	22	2200	Continued medication 100 mg. 2 x week for 2 weeks, then daily
12	2.01	3.57	3.82 (30)	9.9	10.1	12.1 (30)	6	8	10.0	100	21	2100	Continued medication 50 mg. 2 x week
13	1.79	2.81	3.38 (30)	8.7	11.3	13.0 (30)	3	6	10.0	100	30	3000	Continued daily medication
14†	2.97	3.23	3.55 (27)	8.0	10.5	13.4 (27)	3	3	6.6	100	27	2700	Continued daily medication

*Incubated with normal gastric juice before administration.
†This patient also received vitamin C, thiamin, and niacin.

Table 4

acid" parenterally (of these patients, three were classified as having pernicious anemia, one as nutritional anemia and one, indeterminate); while Table 4 indicates results of oral therapy with nine other patients (two classified as pernicious anemia, five nutritional macrocytic anemia and two indeterminate).

With one unexplained exception *(case 7)* all of the patients treated exhibited remission of anemia. Oral administration appeared to be more effective with respect to reticulocyte response and blood regeneration probably, as the authors point out, because of the greater magnitude of dosage. Generally, "folic acid" was found to induce positive responses irrespective of the route of administration and regardless of the clinical classification of pernicious anemia* or nutritional macrocytic anemia.

Comparing the efficacy of the *L. casei* factor with liver extract, the authors observe:

> "It is apparent that in the doses given, folic acid does not produce a reticulocytosis and red cell increase as great as that induced by large amounts of parenteral potent liver extract. Since the time of the response and the clinical alterations parallel the action of liver extract it might be expected that larger doses of folic acid will be fully as effective. Studies have not progressed to the point that would warrant discussion of the relation of folic acid to intrinsic or extrinsic factor. At the present it appears to be an effective hemopoietic agent of itself. It is not to be expected, however, that synthetic folic acid will have a curative effect above and beyond that afforded by potent liver extracts since the original compound was isolated from liver."

Leucopenia: The phenomenon of leucopenia (abnormal decrease in number of leucocytes or white blood cells) is often a concomitant complication of anemia. In their studies on anemia, Vilter *et al* (2) found that "folic acid" stimulated an increase in leucocytes more or less parallelling the increases in hemoglobin and erythrocytes. In an earlier note, Berry, Spies and Doan (5) had reported a temporary rise in the leucocyte count of malnourished patients following intravenous administration of both folic acid concentrates and crystalline *L. casei* factor.

Shortly before crystalline *L. casei* factor became available, Watson, Sebrell, McKelvey and Daft (6) of the University of Minnesota Hospitals and the United States Public Health Service had tested the therapeutic efficacy of potent *L. casei* concentrates on anemia and leucopenia. Encouraged by the established effectiveness of *L. casei* concentrates in treating sulfonamide-induced anemia and leucopenia in rats (7, 8, 9), they attempted the treatment of 17 patients with a similar blood picture, the so-called "refractory" or aplastic anemia and leucopenia. No effect was observed in the eight cases of aplastic anemia nor in one case of leukopenia which had persisted after sul-

*In an earlier study, Castle and associates (4) reported failure of a folic acid concentrate, administered orally, to cause remission in pernicious anemia. This may be because of the small dosages employed, up to 3.6 milligrams per day.

fonamide therapy for infection. Six cases of leukopenia resulting from Roentgen ray therapy for carcinoma and one case of leukopenia resulting from radiation therapy for polycythenia vera (abnormal increase in red blood cells) responded to the "folic acid" concentrates with increased leukocyte counts. The case studies were too limited in number to warrant the drawing of any definite conclusion. The authors reported the findings in order to stimulate further study of the possible effectiveness of "folic acid" in the treatment of certain forms of leukopenia, especially that resulting from radiation therapy.

Sprue: The sprue syndrome is characterized, among other things, by the presence of a macrocytic anemia, and occasionally, a mild leucopenia. Because these blood symptoms, as well as the characteristic fatty stools, diarrhea, marked weight loss and impaired absorption, are closely similar to the manifestations of vitamin M deficiency in monkeys, the possibility of treating sprue with the newly available synthetic *L. casei* factor suggested itself. Last November, Darby and Jones (10) at the Vanderbilt University School of Medicine in Nashville reported on several cases of non-tropical sprue thus treated. The first two patients received intramuscular injections of the synthetic "folic acid" in 15 milligram daily doses as the sole therapeutic measure. Within a few days, the reticulocyte counts rose sharply from pre-treatment levels of about 3-4 per cent to peaks of about 15-16 per cent. Erythrocytes and hemoglobin levels also rose. Definite subjective improvement accompanied the favorable hematologic responses. The symptoms of diarrhea, inflammation of the tongue, soreness of the mouth, disappeared; both patients made good weight gains; glucose and vitamin A blood tolerances approached normal. In a subsequent report, Darby, Jones and Johnson (11) reported follow up studies of the second of these two cases, in which the reticulocyte count rose from 16 per cent on the fourth day of treatment to 43 per cent on the sixth day. A third case of sprue was reported in which treatment with synthetic *L. casei* factor induced similar favorable responses.

In January of this year, Spies, Minnich and Koch of this country reported, in conjunction with Lopez and Menendez of Cuba (12) on the response of tropical sprue to treatment with "folic acid". Studies were conducted at the Calixto Garcia Hospital in Cuba where sprue is endemic. In their preliminary report, these investigators indicated dramatic hematopoietic responses to treatment with synthetic *L. casei* factor in all of three cases studied. These findings were confirmed and extended in a more detailed report which appeared one month later (12a). Reticulocytes increased by the fourth or fifth day and, as reported similarly by Darby and Jones, came to a peak on the sixth day. Red blood cells and hemoglobin rose also and the patients reported a return of strength and well-being and appetite, and an improvement in the nature of the stools. The studies are still underway, as are others

elsewhere, and it is to be expected that the next few months will bring even more clear-cut results in interpretations.

Thymine and Folic Acid:

As this issue goes to press, preliminary evidence has been made available concerning the possibility that thymine may be used clinically as a substitute for folic acid (*L. casei* factor) in the treatment of macrocytic anemia (14).*

Thymine (a pyrimidine compound, not to be confused with the B vitamin, thiamine), is a component of nucleic acid and has long been recognized as an integral part of the living cell. It was shown to be capable of substituting for folic acid as a microbiological growth factor about five years ago (15, 16). Subsequent studies confirmed these original observations, indicating further the high specificity of thymine in this substitution (17, 18, 19, 20). The growth-promoting requirement of thymine, as compared to folic acid, however, was tremendously high, being of the order of 5000 to 1 (20). It was suggested by Stokes (20) that folic acid acts as an enzyme or coenzyme in the synthesis of thymine (or a thymine-like compound) which is used by bacteria to form nucleic acid, a basic cell component. The provision of large amounts of thymine was thought to make possible the direct utilization of thymine as a building block for nucleic acid without the presence of folic acid as a catalyst for its synthesis.

Clinical Use of Thymine: Stokes' hypothesis concerning the replaceability of folic acid by large amounts of thymine in the basic biological processes of microorganisms suggested its use in proportionately large quantities as a substitute for folic acid in the human economy (14). Using the microbiological ratio (5000:1) as a guide, the dosage of thymine required to replace minimal effective daily doses of 2.5 and 5 milligrams of synthetic folic acid was calculated to be 12.5 to 25 grams per day. Because thymine is not at present available in quantities sufficient for administration in this dosage, attempts were made to study its effect in smaller doses. Six patients with nutritional macrocytic anemia and the anemia of sprue were treated with 5 to 50 milligrams of thymine daily for ten days. Results were disappointingly negative. One patient with macrocytic anemia in relapse was selected for trial with larger dosages. This patient had previously been shown to respond to liver extract therapy and to relapse in the absence of such therapy. No spontaneous remissions had been known to occur during the four-year period in which the patient had been studied. Treatment with doses of 500 milligrams of thymine twice daily were ineffective. When the dosage was increased to a total of six grams per day (still less than the calculated requirement of 12.5 to 25 gm.), an increase in reticulocytes was obtained, peak

*cf.—*Borden's Review of Nutrition Research,* February, 1946, "Folic Acid," page 6.

responses occurring on the eleventh day of treatment. Red blood cells and hemoglobin rises followed, reaching peaks on the twentieth day of treatment. The patient exhibited a characteristic subjective improvement as well as relief of symptoms of glossitis.

These findings, based on the response of a single patient, may or may not have important significance in the folic acid-anemia picture. They indicate, however, the importance of further research along these lines and suggest a possible mechanism explaining the action of both thymine and folic acid in the stimulation of blood cell formation through the synthesis of nucleic acid, a basic cell constituent.

Conclusion

The studies reported here constitute the introductory chapter to the story of "folic acid" in the human economy. The rest of the story, even now being unfolded in laboratories and clinics throughout the country, looks extremely promising, but what it will reveal is still largely a matter of conjecture. In a summary of recent clinical experience the statement has been made that synthetic folic acid has a striking anti-anemic effect in five types of macrocytic anemia: pernicious anemia, nutritional macrocytic anemia and the macrocytic anemia of sprue, pellagra and pregnancy (13). Although the mechanisms involved are yet to be explained and the relationship, if any, between folic acid and the erythrocyte maturing factor or its components, the intrinsic and extrinsic factors, is still obscure, it is safe to say that, at the present writing, another milestone in the nutritional management of anemias has been passed.

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NEWS DIGEST

VITAMIN A—New light has been shed on the desirability of increasing the vitamin A content of ordinary diets as a result of animal experiments. Previously shown to be effective in prolonging the "prime of life" period and in increasing the life span of experimental animals, it has now been demonstrated that high dietary levels of vitamin A promote more rapid growth and result in less individual variability within familial groups. This indicates that liberal vitamin A intakes are capable of exerting both a stimulating and stabilizing influence in growth patterns. The effects noted were obtained with vitamin A intake levels ranging from two to four times those considered optimum for ordinary, normal requirements. *Science News Letter,* July 28, 1945.

NUTRITION OF SCHOOL CHILDREN—Indications of unfavorable nutrition conditions among school age children have been obtained from an extensive survey throughout Florida conducted last year. The results are considered more or less typical in other rural and urban areas throughout the country. Over two thousand children in the first twelve grades were examined and showed a fairly high incidence of specific nutritional deficiencies, despite such favorable environmental conditions as sunshine and easily available fresh produce. In some sections well over 50 per cent of the children showed at least slight signs of rickets and also indications of vitamin C deficiency. In one isolated rural area 50 per cent of those examined had gum signs indicative of a lack of vitamin C. The frequency with which signs suggestive of other deficiency states such as the roughened skin or granulated eyelids of vitamin A deficiency and the angular stomatitis indicating riboflavin need was as high as 64 per cent for vitamin A and 85 per cent in the case of riboflavin in some of the nutritionally poorest groups. Anemia was not encountered as frequently in these children as the more specific entities, although the hemoglobin levels of Negro children were found to be generally lower than those of the white children in the same area. A concurrent dietary survey was made to determine the types of foods eaten by Florida school children. The information secured by this means corroborated the observations made on the children themselves. Not only were many valuable types of foods such as colored vegetables, citrus fruits and milk missing from the diet lists of a goodly proportion of the children questioned, but the reports show also that many children go without one meal during the day, usually the breakfast, or eat a breakfast which is very inadequate. Facts of similar import are revealed from a national survey of children's diets. It was found that a distressingly high percentage of children from all types of homes receive meals which are poorly selected. Plans and funds for an expanded national school lunch program are expected to aid materially in improving the nutritional status of school children in local communities throughout the country. *J. Am. Med. Assoc., 128,* 1233 (1945).

FROZEN MEALS—One of the major airlines has recently announced the serving aloft for the first time of pre-cooked "frozen" meals. The new plan, developed over a six year period of tests, enables service of oven-hot meals while flying over the ocean at 300 miles per hour. The food is cooked to the proper degree at a ground plant. It is then placed in a partitioned

plate, flash-frozen at 20 degrees below zero and kept at a temperature not exceeding 10 degrees above zero. Each plate is wrapped in Patapar paper and sealed in a laminated paper envelope.

Before departure the packaged meals are placed in a pre-chilled balsa wood box covered with stainless steel. They are kept frozen 48 hours, or longer if dry ice is used. Two electronic ovens defrost and produce 12 piping-hot home-style meals every 15 minutes. *N. Y. World-Telegram,* March 21, 1946.

VITAMINS IN ICE CREAM—That ice cream is not only a good source of two important vitamins, but compares favorably with, or even exceeds many other nutritionally important foods in those vitamins has been demonstrated. Samples of coffee, maple and vanilla ice cream were assayed for carotene (pro-vitamin A), riboflavin and ascorbic acid. The results were fairly uniform for all of the flavors, averaging 0.10 milligram of carotene and 0.26 milligram of riboflavin per 100 grams of ice cream. No ascorbic acid was found, presumably because it is lost through the incorporation of large amounts of air in commercial ice creams. The particular vitamin values of ice creams, of course, vary with the nature and amount of the ingredients used and the process of manufacture. Comparison with whole milk and with green leafy vegetables indicated the ice cream samples in question to be a superior source of carotene. Although ice cream on a weight basis is even richer than milk in riboflavin, it is, under practical conditions of purchase by volume, a lesser source of riboflavin than an equal volume of milk. Ice cream was found also to be somewhat richer in riboflavin than eggs, a superior source of the vitamin; about equal in riboflavin content to various meats, (beef round, pork loin, veal chop, leg of lamb), chicken leg, and oysters; and superior to whole-wheat bread, chicken breast, salmon. Of about 50 common fruits and vegetables only broccoli approached ice cream in riboflavin value and only six or eight of the others contained half as much riboflavin. It has been estimated that the retail value of the ice cream consumed in this country annually is about one-fourth that of milk and over twice that of eggs, apples or potatoes. On this basis of consumption, together with the favorable comparison with numerous types of common foods, ice cream may be considered an excellent dietary source of carotene and riboflavin. *New England J. Med. 234,* 47 (1946).